M-I-(1) Scientific abstract

The proposed phase 1 study entitled: "Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the $VEGF_{121}$ cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease" utilizes the identical Ad_{GV}VEGF121.10 vector that is approved by the Food and Drug Administration (FDA) for the treatment of coronary artery disease under RAC#9711-211, "Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the $VEGF_{121}$ cDNA to the Ischemic Myocardium of Individuals with Life Threatening Coronary Artery Disease" that was discussed by the RAC at the December 9, 1997 meeting.

Ad_{GV}VEGF121.10, is an FDA approved biologic product for the administration to the myocardium of individuals with coronary artery disease. In this clinical protocol, Ad_{GV}VEGF121.10 is intended to treat patients with peripheral vascular disease, a condition associated with atherosclerosis of the lower extremities, and reduced blood flow to the heart. The proposed study utilizes a replication deficient adenovirus vector Ad_{GV}VEGF121.10 coding for the human vascular endothelial growth factor 121 ($VEGF_{121}$) cDNA. By expressing the $VEGF_{121}$ cDNA in the ischemic lower limb, the study is designed to evaluate the concept that $VEGF_{121}$ cDNA will induce angiogenesis, bypassing areas of obstruction in the arteries. The proposed clinical protocol is a randomized double blinded, dose-escalating study involving a total of 40 individuals that is divided into 2 parts: A and B. Part A is a dose escalating safety/toxicity study of 20 individuals with lower limb claudication, where no surgery is contemplated for at least >6 months. Part B will include 20 individuals that have limb threatening ischemia where surgery is not possible. Two types of controls are built into Parts A and B of the study. First, each individual will serve as their own control before and after therapy. Second, in each dose group of n=4, 1 of the 4 individuals (in a double blind, randomized basis) will receive the vector diluent, and 3 of 4 individuals will receive the Ad_{GV}VEGF121.10 vector. The total doses for Parts A and B will range from $4x10^8$-$4x10^{10}$ particle units. All groups will be assessed with a variety of safety and efficacy parameters relevant to peripheral vascular disease. The following objectives will be met: (1) To determine the dose-dependent safety/toxicity of direct administration of the vector Ad_{GV}VEGF121.10 to the ischemic lower limb; and (2) To demonstrate whether direct administration of Ad_{GV}VEGF121.10 to the lower limb will induce growth of collateral blood vessels, improve blood flow, and improve function in the region of ischemia.